Review Article

Strategies in Computer Aided Drug Design

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ABSTRACT

Drug design is an iterative, time consuming and costly research process. Computer aided drug design (CADD) provides several tools and techniques that helps in various stages of drug design thus reducing the cost of research and development time of the drug. In this paper we present the areas where CADD tools support drug discovery process, drugs available in the market designed using these tools, the stages in the process of drug discovery and the compound success rate in different states of drug discovery process.

Keywords: Computer aided drug design, Drug discovery process, Homology modeling, Lead optimization.

INTRODUCTION

Computer aided drug design (CADD) is an evolving cascade of research area encompassing many facets. The cost and time invested by the pharmacological research laboratories are heavy during the various phases of drug discovery, starting from therapeutic target identification[1,2], candidate drug discovery, drug optimization through pre clinical and extensive clinical experiments to assess the effectiveness and safety of newly developed drugs. In recent years with the development of genomic investigations many new disease targets are identified.

The major pharmaceutical companies have invested heavily in the routine ultra-High Throughput Screening (uHTS) of vast numbers of 'drug-like' molecules[3,4].

In parallel with this, drug design and optimization increasingly uses computers for virtual screening[5-7].

Recent advancements in DNA microarray experiments explore thousands of genes involved in a disease can be used for gaining in depth knowledge about the disease targets, metabolic pathways and toxicity of the drugs[8]. Rest of the paper is organized as follows.

Section II gives the drug discovery process, Section III gives the areas where CADD tools and techniques support the drug discovery process and summary is given in Section IV.

Drug Discovery Process

Drug discovery is a series of processes which when followed identify the drug compounds for the effective treatment or control of disease targets. It starts with the screening of large number of chemical compounds to optimize the disease targets.

It requires insight information about the structure of the drug receptor so that the drug molecules can be adjusted to the binding site of the protein. Fig 1 shows the steps to be followed in order to discover a new drug.

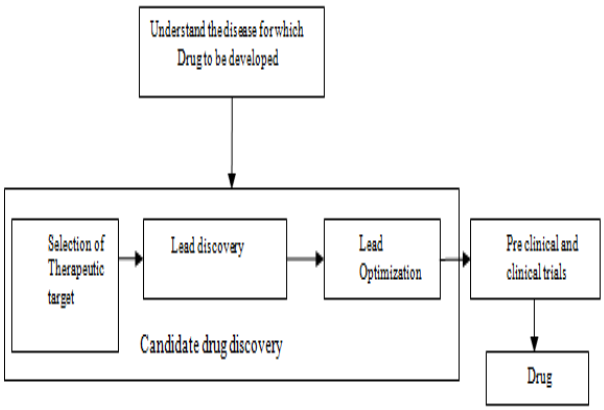

Figure 1: Drug Discovery Process

Drug discovery process starts with understanding the disease for which the drug to be designed. It consists of the following steps.

Candidate Drug Discovery

Selection of Therapeutic Target

Lead Discovery

Lead Optimization

Pre clinical and clinical trials to evaluate the safety, efficacy and adverse effects of the drug

Animal Studies

Clinical Trials

FDA approval process for the newly discovered drug and bringing the drug to market for public use.

Additional post marketing testing and further improvement of the drug.

In general, it takes 3-6 years for new drug discovery and pre-clinical development. The clinical trials can last up to 10 years or more before the product reaches the market[9].

Approximately it takes 12-15 years (refer fig 2) and costs more than $1.3 billion to bring a successful drug to market[10].

On an average, among the 5000-10000 screened compounds about 250 compounds are selected for preclinical trials. From them only 5 survive to enter into clinical trials while only one approved by the FDA after strenuous review of the newly discovered drug.

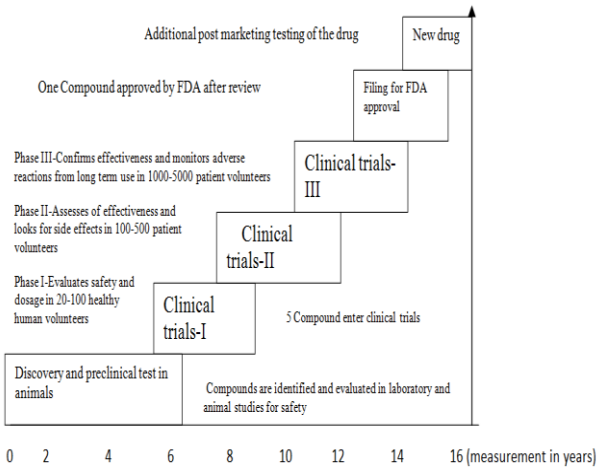

Figure 2: Steps in Drug Discovery

Computer Aided Drug Design

CADD methods and bioinformatics tools offer significant benefits namely cost savings, reduction in time to bring the drug to market, to know in depth about the drug receptor interactions thus providing further improvement in existing drugs.

There are several key areas where CADD supports in designing an effective drug.

- Virtual High Throughput Screening (vHTS). vHTS is a method for searching new lead molecules to develop into a promising drug for the selected disease target. In vHTS, small molecules of the drug like compounds stored in the database are screened against the protein targets to find which molecules can bind strongly to the target protein[11]. They are called lead molecules for the particular disease. These lead molecules are then extracted from the database for further testing. With the efficient CADD screening tools available nowadays time and the expenditure required for finding a promising lead molecule is considerably less than traditional methods.
- Sequence Analysis. The insight knowledge about the amino acid sequence of protein molecules of various organisms is essential for a design of the successful drug. Many sequence analysis tools and algorithms developed by CADD researchers helps in finding out the similarity among the species based on the proteomic and genomic sequences. This sequence similarity information is useful in assuming the relationships among the various organisms involved in the study.
- Homology Modeling**.** As most of the drug targets are proteins, scrupulous knowledge about the three dimensional structure of those protein molecules is essential during drug design. Very few 3-D structures of protein molecules are available in realism. However 3-D structures of protein molecules can be predicted using CADD techniques. As it is proved that many protein molecules have similar amino acid sequences. If a 3-D structure of a protein molecule is known, this structure is used to predict the 3-D structure of the protein molecules which have high similarity scores with the matching protein molecules. This process is known as homology modeling. Many database like, SWISS MODEL[12] repository having predicted 3-D protein structures, are created using CADD homology modeling techniques.
- Similarity Searches. A common activity during drug discovery is the search for drug analogues. Starting with an existing promising lead molecule of a drug, chemical compounds with similar protein structure (2D or 3D), common amino acid sequences or electro static properties etc can be searched using the CADD tools from existing proteomic and genomic databases. These drug analogues can be further tested to bring an improved drug candidate as an alternative for the existing drug.
- Physicochemical Modeling**:** Drug-receptor interactions occur on atomic scales. The physicochemical properties such as hydrophobicity and polarity of the drug and target have a intense effect of how candidate drugs bind to protein targets. As the drug and the target interactions occur on atomic scales the study of bio chemical and biophysical properties of them provide an in depth understanding about these interactions.
- Drug Optimization**:** When a promising candidate drug has been found during the drug discovery process, then the newly discovered drug has to be optimized to increase its affinity and binding towards target protein. This can be carried out by modifying the structure of the drug. Alternate templates or scaffolds like the newly discovered drug are evaluated in this stage to find out a promising drug for the disease target. The metabolic and toxic properties of the candidate drug are optimized to increase the potential of the drug.
- ADMET properties of a drug: The key characteristics for drugs are Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET). These properties are called as the bioavailability and bioactivity of the drug. Most of the candidate drugs fail in clinical trials because of the problems of the toxicity and metabolism of the drugs in human beings which makes useless the billions of dollars and years of

research spent up to this phase. Even though these properties should be measured in the lab, they can also be predicted in advance using CADD tools which save the years of research and the huge money spent for the experiments on the candidate drug.

Table 1 shows a list of software that supports some key areas in designing a candidate drug.

While Table 2 shows a list of successful drugs in market designed using CADD techniques.

Table 1: Software that supports some key areas during drug design process

S. No	Area of Research	Software
1.	Docking	ZINC, Autodock, Dock, Gold, LigandFit, Dock blaster
2.	Ligand design	Gandi, Sprout, FlexNovo
3.	QSAR	cQSAR, clogP, Galahad
4.	ADMEToxicity	QikProp, Q-ADME, ADMET Predictor
5.	Lead optimization	Wabe
6.	Physicochemical modeling	Swiss-PDB

Table 2: Successful Drugs in Market designed using Cadd Techniques

S. No	Drugs	Inhibits
1.	Amprenavir (Agenerase)	HIV Protease
2.	Nelfinavir (Viracept)	HIV Protease
3.	Zenamivir (Relenza)	Neuraminidase
4.	Tomudex	Thymidylate Synthase
5.	Imitinab mesylate (Gilvec)	Abityrosine kinase

CONCLUSION

Computer aided drug design (CADD) is a multidisciplinary field attracting the researchers from information technology, medicine, pharmacology etc. to discover new tools and techniques or enhance the available tools and techniques to assist in drug discovery process.

These techniques proved to be effective in various stages of drug discovery process thus reducing both cost and time taken for developing a drug than conventional methods.

Various CADD tools that assist during the process of drug development are provided with few examples of the drugs that are available in the market which were successfully designed using these tools.

These tools can be used, enhanced to assist the various phases of drug discovery.

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